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Intraoperative perineural hyaluronic acid injection does not improve outcomes after carpal tunnel release in moderate-to-severe CTS: a retrospective cohort study

Mustafa Dinç[1], Ömer Cevdet Soydemir[1], Recep Karasu[1], Bilal Aykaç[1], Hünkar Çağdaş Bayrak[2]

[1]*Department of Orthopedics and Traumatology, Bursa City Hospital, Bursa, Turkiye*

[2]*Department of Orthopedics and Traumatology, Çekirge State Hospital, Bursa, Turkiye*

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ABSTRACT

Aims: This study aims to evaluate whether intraoperative perineural hyaluronic acid (HA) injection provides additional clinical or electrophysiological benefits beyond standard carpal tunnel release (CTR) in patients with moderate-to-severe carpal tunnel syndrome (CTS).

Methods: In this retrospective cohort study, 130 patients with electrophysiologically confirmed moderate-to-severe CTS underwent either CTR alone (n=66) or CTR with intraoperative perineural HA injection (n=64). HA (Alsegovisc®, 40 mg/2 ml, 1500 kDa) was administered following surgical decompression. Outcomes included pain (Visual Analog Scale, VAS), symptom severity and function (Boston Carpal Tunnel Questionnaire, BCTQ), sensory and motor conduction (SNCV, DML), and achievement of patient-centered benchmarks (minimal clinically important difference, MCID; patient acceptable symptom state, PASS). Evaluations were carried out pre-surgically and at 3- and 6-month intervals following the procedures.

Results: Both groups demonstrated significant improvements in pain (VAS: 7.0 to 2.0), symptom severity (BCTQ-SSS: 45.0 to 18.0), function (BCTQ-FSS: 34.5 to 13.5), and electrophysiological parameters (SNCV: 31.4 to 40.5 m/s; DML: 5.5 to 4.2 ms) over 6 months (all $p<0.001$). However, The comparison did not yield statistically significant results between groups at any time point ($p>0.05$), and effect sizes were consistently small (Cohen's $d<0.2$). MCID and PASS thresholds were met by >68% of patients in both groups. Subgroup analyses revealed no predictive value for baseline disease severity or thenar atrophy.

Conclusion: Intraoperative perineural HA injection did not confer additional clinical or electrophysiological benefit over CTR alone in moderate-to-severe CTS. Despite compelling preclinical data, HA's efficacy may be attenuated in chronic fibrotic nerve compression due to pharmacokinetic and tissue-level limitations. These findings do not support routine use of intraoperative HA in advanced CTS but highlight the need for future prospective trials targeting earlier-stage disease, sustained-release formulations, or repeated dosing strategies.

Keywords: Carpal tunnel syndrome, hyaluronic acid, perineural injection, carpal tunnel release, moderate to severe neuropathy

INTRODUCTION

Among peripheral nerve entrapment disorders, carpal tunnel syndrome (CTS) is the most frequently diagnosed, occurring due to compression of the median nerve within the carpal tunnel at the wrist, leading to nerve ischemia, axonal injury, and progressive functional impairment.[1,2] While nonsurgical treatments such as splinting, corticosteroid injections, and activity modification are recommended for mild-to-moderate cases, these approaches typically provide only transient symptomatic relief and often fail to prevent progression of disease.[3,4] According to recent longitudinal studies, 57%–66% of patients eventually require surgical intervention following one to three years of conservative management.[3,5-7]

Surgical decompression via carpal tunnel release (CTR) is widely accepted as the definitive treatment for moderate-to-severe CTS.[8,9] Although most patients experience significant symptom resolution, clinical outcomes are not universally favorable. Up to 25% of patients report suboptimal recovery, and approximately 8% may experience worsening of symptoms following surgery.[7,10] Factors contributing to incomplete recovery include chronic perineural fibrosis, ischemia-induced nerve degeneration, and long-standing compression—all of which may limit the nerve's regenerative capacity even after mechanical decompression.[2,11,12] In this context, there is growing interest in identifying biologic

Corresponding Author: Mustafa Dinç, drindianster@gmail.com

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adjuncts that could enhance surgical outcomes, particularly in patients with advanced disease.

Several injectable therapies—including corticosteroids, platelet-rich plasma (PRP), and 5% dextrose—have been studied as potential nonsurgical treatments for CTS. These agents are believed to exert anti-inflammatory, antifibrotic, or neuroregenerative effects, and have shown modest clinical benefits in patients with mild-to-moderate CTS.[10,13,14] However, their application during or alongside surgical treatment remains poorly studied, and evidence supporting their use in patients with moderate-to-severe CTS is lacking.

Hyaluronic acid (HA), a naturally occurring glycosaminoglycan, has recently attracted attention as a potential perineural adjunct due to its anti-inflammatory, antifibrotic, and neuroprotective properties. Preclinical studies have demonstrated that HA can reduce perineural adhesion, inhibit fibroblast proliferation, and promote axonal regeneration in models of acute nerve injury.[15-17] Despite this promising biologic rationale, clinical investigations on the use of HA in CTS remain scarce, particularly in the setting of surgical decompression. To date, only a few small studies have evaluated perineural HA injections, most of which were limited to mild-to-moderate CTS and used HA as a stand-alone treatment rather than as an intraoperative adjunct.[18]

Therefore, the primary goal of this research was to assess whether the intraoperative administration of perineural HA during CTR could enhance clinical and electrophysiological recovery in patients with moderate-to-severe CTS. Given the limited regenerative capacity of chronically compressed nerves and the lack of data on HA's use in this context, we hypothesized that combining HA with surgical decompression might accelerate recovery and improve functional outcomes compared to CTR alone.

METHODS

Ethics

The study was designed as a retrospective cohort investigation and performed at Bursa City Hospital's Department of Orthopedics. This study adhered to the ethical guidelines of the Declaration of Helsinki and approved by the Bursa City Hospital Scientific Researches Ethics Committee (Date: 05.03.2025, Decision No: 2025-5/2).

Patient Selection

Patients above 18 years old who underwent primary unilateral CTR, with or without intraoperative perineural HA injection, between January 1, 2020, and September 30, 2024, at our institution were screened for inclusion. Eligible participants were required to have a diagnosis of moderate-to-severe CTS, as verified through nerve conduction studies, and to have completed a minimum of six months of postoperative clinical and electrophysiological follow-up. The diagnosis of CTS was established according to CTS was based on symptoms persisting for more than three months and characterized by paresthesia or dysesthesia in the median nerve distribution, typically exacerbated by repetitive wrist activity or occurring at night, with relief upon postural adjustment or hand-shaking. In addition, patients were required to exhibit at least one of the following objective signs: such as reduced sensation along the median nerve pathway, weakness or atrophy of the thenar muscles, or a positive response to Phalen's or Tinel's test.

Exclusion criteria comprised individuals with bilateral CTS, a history of prior wrist surgery or perineural injection, or comorbid conditions known to affect peripheral nerve function, including diabetes mellitus, rheumatoid arthritis, systemic infections, malignancy, cervical radiculopathy, thoracic outlet syndrome, or peripheral polyneuropathy. Additional exclusion criteria included hematologic abnormalities such as thrombocytopenia or platelet dysfunction, and pregnancy. After the application of these criteria and verification of complete follow-up data, 130 patients met the eligibility criteria and were incorporated into the final analytical cohort.

CTS Grading

Electrophysiological diagnosis and grading were performed according to the Padua classification.[19] Moderate CTS was defined as abnormal sensory nerve conduction velocity (SNCV) and prolonged distal motor latency (DML). Severe CTS was defined by the absence of SNCV and prolonged DML.

Group Allocation and Surgical Procedure

Patients were retrospectively evaluated in two groups based on whether they had previously received adjunctive intraoperative perineural HA injection alongside standard CTR. Group 1 (CTR group, n=66) underwent standard open CTR, while group 2 (CTR+HA group, n=64) received the same surgical decompression combined with an intraoperative perineural HA injection. All procedures were performed by one of three senior orthopedic surgeons using a standardized open technique under local anesthesia. Total release of the transverse carpal ligament followed by confirmation of adequate decompression of the median nerve, patients in the CTR+HA group received a perineural injection of 2 ml high-molecular-weight HA (Alsegovisc; 40mg/2ml, 1500 kDA) directly around the median nerve before wound closure. To ensure retention of the HA solution, the surgical wound was closed meticulously using continuous, watertight suturing of both the subcutaneous and cutaneous layers. The CTR-only group received no additional biologic agent. Postoperative care was standardized for both groups and included wrist splinting for seven days, followed by early resumption of light activities as tolerated.

Outcome Measures

Assessments were conducted at three time points: immediately before the surgical procedure and HA injection (baseline), and at 3 and 6 months postoperatively. These evaluations included both clinical and electrophysiological parameters to comprehensively assess treatment efficacy over time.

Primary Outcomes

Pain severity was measured using the Visual Analog Scale (VAS), providing a quantitative evaluation of patients' perceived pain levels. Functional status and symptom burden were assessed using the Boston Carpal Tunnel Questionnaire (BCTQ), which comprises two subscales: the symptom

severity scale (BCTQ-SSS) and the functional status scale (BCTQ-FSS). Clinical success was defined as the proportion of patients achieving the MCID for VAS and BCTQ scores.[20] These MCID thresholds were calculated using an anchor-based approach, incorporating receiver operating characteristic (ROC) curve analysis anchored to a 5-point global satisfaction item. Additionally, the PASS was evaluated using established cutoff values for VAS and BCTQ outcomes, reflecting patients' perception of symptom resolution to an acceptable level.

Secondary Outcomes

Electrophysiological parameters: SNCV and DML were recorded using standardized techniques.[21] SNCV was measured over a 14 cm segment from the second interphalangeal joint to the wrist. DML was measured from a stimulation point 8 cm proximal to the abductor pollicis brevis. The average of three readings was used for each parameter.

Statistical Analysis

The data analyses were carried out using IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA). Prior to the study, A preliminary power calculation was performed with G-power software (version 3.1.9.7), based on mean and standard deviation values reported in comparable published studies. Assuming a medium effect size (Cohen's d=0.5), a minimum sample size of 128 participants was determined to be necessary to achieve 90% power at a significance level of 0.05. With a total of 130 patients included, Although the study was sufficiently powered to detect clinically relevant differences, no statistically significant variations were found between the treatment groups.

The normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Data that followed a normal distribution were expressed as mean±standard deviation (SD), while those not normally distributed were presented as median and interquartile range (IQR). Categorical variables were described as frequencies and percentages. Comparisons between the CTR and CTR+HA groups were made using the independent samples t-test for normally distributed data and the Mann–Whitney U test for non-normally distributed data. The Chi-square test was applied for categorical variables. Effect sizes were calculated using Cohen's d for parametric data and the r value for non-parametric comparisons.

An anchor-based approach was employed to determine the MCID and PASS thresholds for VAS and BCTQ scores. A five-point global patient satisfaction scale served as the anchor, with responses ≥4 classified as "responders" for MCID and "satisfied" for PASS analyses. The validity of this anchor was confirmed by Spearman's correlation with the corresponding clinical change scores. ROC curve analysis was used to identify MCID and PASS thresholds, with sensitivity, specificity, and area under the curve (AUC) values reported.

Finally, a binary logistic regression model was applied to determine which baseline variables independently predicted the likelihood of achieving a clinically meaningful improvement. Independent variables included age, sex, symptom duration, electrophysiological severity, and the presence of thenar atrophy. Odds ratios (OR) were reported along with their 95% confidence intervals (CI) and associated p-valueswere reported for each predictor.

RESULTS

A total of 130 patients met the inclusion criteria and were included in the final analysis: 66 in the CTR group and 64 in the CTR+HA group. As summarized in **Table 1**, there were no statistically significant differences between groups in age, symptom duration, gender distribution, hand dominancy, electrophysiological severity (Padua classification), thenar atrophy grade, or final satisfaction levels (p>0.05 for all). This indicates that the groups were comparable at baseline.

Table 1. Comparison of baseline demographic and clinical characteristics between the CTR and CTR+HA groups

	CTR n: 66	CTR+HA n: 64	p value	Effect size
Age	57.0 (44.5–63)	51.5 (43–61.5)	0.244*	0.107
Duration	15.0 (6–18)	11.0 (7.25–16.75)	0.496*	0.063
Gender: male/female	15/51	21/43	0.276**	
Dominancy, yes/no	35/31	34/30	0.991**	
Padua				
Moderate	37	41	0.452**	
Severe	29	23		
Thenar atrophy				
None	18	22	0.634***	
Mild	22	23		
Moderate	16	13		
Severe	10	6		
Final satisfaction question				
1. Very dissatisfied	1	1	0.973***	
2. Dissatisfied	4	5		
3. Moderate	6	4		
4. Satisfied	26	25		
5. Very satisfied	29	29		

Values are presented as median (interquartile range) for continuous variables and as frequencies for categorical variables. The normality of data distribution was assessed using the Kolmogorov–Smirnov test. Continuous variables were compared using the Mann–Whitney U test (*), while categorical variables were analyzed using the Chi-square test (**) or the Monte Carlo simulation method (***), as appropriate. CTR: Carpal tunnel release, HA: Hyaluronic acid

Post hoc effect size calculations yielded low values, suggesting that any treatment effect, if present, was likely too small to be clinically relevant. In other words, the similarity in outcomes across groups indicates that both interventions exerted comparable effects within this sample.

Both groups showed significant within-group improvement in pain (VAS) and symptom severity/function (BCTQ-SSS, BCTQ-FSS) at 3 and 6 months postoperatively. However, no statistically significant differences were found between the CTR and CTR+HA groups at any time point. Effect sizes were small, further suggesting limited between-group differences (**Table 2**).

No statistically significant differences were observed between the CTR and CTR+HA groups in SNCV or DML at any time point. Both groups showed within-group improvements, particularly in SNCV, but intergroup comparisons yielded p-values > 0.05 and small effect sizes (**Table 3**).

As shown in **Table 4**, clinically meaningful thresholds for the MCID and PASS were established using an anchor-based approach. A 5-point global satisfaction item served as the external anchor, with scores ≥4 indicating both MCID

Table 2. Comparison of clinical outcomes (VAS and BCTQ scores) between CTR and CTR+HA groups at each follow-up

	CTR (n:66)	CTR+HA (n:64)	p value	Effect size
VAS pre	7.0 (6–8)	7.0 (6–7.75)	0.321*	0.087
VAS 3 months	3.0 (2–4)	3.0 (2–4)	0.801*	0.022
VAS 6 months	2.0 (2–3)	2.0 (2–3)	0.904*	0.011
BCTQ severity preop	45.0 (40–50)	45.5 (38.25–49.75)	0.880*	0.013
BCTQ severity 3 months	28.0 (24–32)	28.0 (23.25–32)	0.561*	0.051
BCTQ severity 6 months	20.0 (16–23.25)	18.0 (14–23)	0.161*	0.123
BCTQ function preop	34.5 (31.75–37.25)	34.0 (30.25–37)	0.307*	0.090
BCTQ function 3 months	21.0 (18–24)	21.0 (19–25)	0.528*	0.055
BCTQ function 6 months	15.0 (11–17)	13.5 (11–17)	0.339*	0.084

Values are presented as median (interquartile range). Group comparisons were performed using the Mann–Whitney U (*) test due to non-normal distribution of the data. VAS: Visual Analog Scale, BCTQ: Boston Carpal Tunnel Questionnaire, CTR: Carpal tunnel release; HA: Hyaluronic acid

Table 3. Comparison of electrophysiological outcomes—sensory nerve conduction velocity (SNCV) and distal motor latency (DML)—between the CTR and CTR+HA groups at baseline, 3 months, and 6 months

	CTR (n: 66)	CTR+HA (n: 64)	p value	Effect size
SNCV preop (m/s)	31.39±3.65	32.03±3.79	0.326**	0.173
SNCV 3 month (m/s)	37.45±3.75	38.22±4.27	0.277**	0.192
SNCV 6 month (m/s)	40.45 (37.58–42.63)	40.95 (39.40–43.40)	0.236*	0.104
DML preop (ms)	5.48±0.64	5.46±0.60	0.807**	0.043
DML 3 month (ms)	4.71±0.68	4.65±0.65	0.616**	0.048
DML 6 month (ms)	4.21±0.70	4.15±0.68	0.660**	0.077

Values are expressed as mean±standard deviation for normally distributed variables and as median (interquartile range) for non-normally distributed variables. Statistical analysis was conducted using the independent samples t-test for normally distributed data and the Mann–Whitney U test for non-parametric data. * Mann–Whitney U test; ** Independent samples t-test. SNCV: Sensory nerve conduction velocity, m/s: Meters per second, DML: Distal motor latency, ms: milliseconds, CTR: Carpal tunnel release, HA: Hyaluronic acid

Table 4. Receiver operating characteristic (ROC) analysis results for determining minimal clinically important difference (MCID) and patient acceptable symptom state (PASS) thresholds

Outcome measure	MCID threshod	AUC (MCID)	Sensitivity (MCID)	Specificity (MCID)	PASS threshold	AUC (PASS)	Sensitivity (PASS)	Specificity (PASS)
VAS	3.5	0.965	0.954	0.857	2.5	0.934	0.817	0.952
BCTQ symptom severity	17.5	0.890	0.917	0.762	23.5	0.902	0.881	0.762
BCTQ functional status	16.5	0.832	0.780	0.714	16.5	0.811	0.761	0.714

Cut-off thresholds were derived using a 5-point satisfaction scale as an anchor; AUC, sensitivity, and specificity are reported for each outcome measures. MCID: Minimal clinically important difference, PASS: Patient acceptable symptom state, AUC: Area under the curve, VAS: Visual Analog Scale, BCTQ-SSS: Boston Carpal Tunnel Questionnaire–Symptom Severity Scale, BCTQ-FSS: Boston Carpal Tunnel Questionnaire–Functional Status Scale

responder status and achievement of PASS. ROC curve analysis was used to define cut-off values for VAS and BCTQ.

As shown in Table 5, a substantial proportion of patients in both groups met the established MCID and PASS thresholds for VAS, BCTQ Symptom Severity, and BCTQ Functional Status at the 6-month follow-up. Although rates were slightly higher in the CTR+HA group, the differences were not statistically significant.

A binary logistic regression analysis was conducted to evaluate which variables independently predictors of clinically meaningful improvement based on MCID thresholds. None of the examined variables—including age, sex, symptom duration, hand dominancy, thenar atrophy, or electrophysiological severity—reached statistical significance. However, patients with severe CTS (Padua classification) demonstrated a non-significant trend toward higher odds of improvement compared to those with moderate CTS (OR: 2.683, p=0.137). These findings suggest that baseline demographic and clinical characteristics were not reliable predictors of treatment response in this cohort (Table 6).

Table 5. Percentage of patients achieving minimal clinically important difference (MCID) and patient acceptable symptom state (PASS) at 6 months

6 months follow-up		PASS	MCID
CTR	VAS	69.7%	80.3%
	BCTQ symptom severity	75.8%	78.8%
	BCTQ functional status	63.6%	68.8%
CTR+HA	VAS	68.8%	84.4%
	BCTQ symptom severity	79.7%	82.8%
	BCTQ functional status	73.4%	71.2%

Proportion of patients achieving MCID and PASS thresholds at 6-month follow-up. MCID: Minimal clinically important difference, PASS: Patient acceptable symptom state, VAS: Visual Analog Scale, BCTQ: Boston Carpal Tunnel Questionnaire, CTR: Carpal tunnel release, HA: Hyaluronic acid

Table 6. Logistic regression analysis of predictors for achieving MCID-level improvement at 6-month follow-up

Variable	OR	p-value	95% CI
Sex (male)	0.435	0.185	0.127-1.490
Dominancy (right)	0.597	0.330	0.212- 1.685
Padua (severe)	2.683	0.137	0.730- 9.860
Thenar atrophy: mild	0.378	0.398	0.040- 3.608
Thenar atrophy: moderate	1.587	0.574	0.317- 7.936
Thenar atrophy: severe	1.343	0.695	0.308- 5.860
Age	0.975	0.286	0.929- 1.022
Symptom duration	0.996	0.924	0.924- 1.074

Binary logistic regression was performed to identify independent predictors of achieving minimal clinically important difference (MCID) at 6 months. Odds ratios (ORs), 95% confidence intervals (CIs), and corresponding p-values are presented. MCID is defined as the smallest improvement in outcome score perceived as beneficial by the patient

DISCUSSION

This study evaluated whether the addition of intraoperative perineural HA injection offers any clinical or electrophysiological advantage over conventional CTR in patients with moderate-to-severe CTS. Both treatment groups exhibited significant improvements in pain, symptom severity, functional status, and nerve conduction measures at the 3-and 6-month follow-ups. confirming the effectiveness of surgical decompression in this population.

However, our findings indicate that the addition of HA did not provide a statistically or clinically meaningful benefit over CTR alone. Across all outcome measures including VAS scores and BCTQ subscales both groups showed comparable trajectories of improvement. Although minor numerical trends favored the HA group in certain metrics, such as functional recovery and symptom resolution, these differences did not reach significance and were associated with small effect sizes.

In addition, electrophysiological recovery, as measured by SNCV and DML, also improved in both groups, with no significant between-group differences at any time point. The slight advantage in SNCV observed in the HA group was not sufficient to suggest a clinically relevant effect of HA on nerve healing.

Patient-centered thresholds MCID and PASS were achieved by a high proportion of patients in both groups. Slightly more patients in the HA group met these benchmarks, particularly for functional outcomes; however, these differences did not achieve statistical significance and should be interpreted with caution.

Also subgroup analyses and logistic regression modeling failed to identify any baseline clinical or demographic factors including age, sex, symptom duration, electrophysiological severity, or thenar atrophy that predicted the likelihood of achieving meaningful clinical improvement. While patients with severe CTS appeared to have a trend toward better outcomes, this did not reach significance, suggesting that HA's impact, if any, is not modulated by disease severity or patient profile.

Overall, these results suggest that while CTR is consistently effective in treating moderate-to-severe CTS, intraoperative perineural HA injection does not confer additional clinical benefit under the conditions evaluated in this study.

The results of our study are consistent with the limited clinical evidence evaluating the use of HA in CTS. Notably, the randomized controlled trial by Su et al.[18] remains the only high-quality clinical investigation to assess HA's therapeutic effect in this context. In that study, ultrasound-guided perineural HA injections were administered to patients with mild-to-moderate CTS. While transient symptom relief was observed at two weeks, no significant improvements were detected in pain intensity, functional outcomes, or electrophysiological parameters at 1, 3, or 6 months. Our findings mirror these results, extending them to a different clinical setting—moderate-to-severe CTS treated with intraoperative HA injection during CTR—demonstrating similarly negligible long-term benefits.

In contrast, preclinical data on HA present a more favorable narrative. Multiple animal studies have reported that HA exerts beneficial effects on nerve healing through reduction of perineural fibrosis, facilitation of axonal regeneration, and preservation of nerve conduction properties.[15-17,22,23] These effects are mediated through several mechanisms, including inhibition of fibroblast proliferation, modulation of inflammatory cytokine activity, and promotion of extracellular matrix homeostasis. However, these studies have generally employed models of acute nerve injury such as crush or transection with immediate post-injury application of HA, in environments not yet subjected to chronic fibrotic remodeling.

The translational discrepancy between experimental models and clinical outcomes is likely attributable to the pathophysiological complexity of chronic CTS. In human patients, the median nerve is exposed to sustained mechanical compression, impaired microvascular perfusion, and a chronically inflamed and fibrotic subsynovial connective tissue.[24] These features may obstruct HA diffusion, reduce receptor binding and ultimately limit its anti-inflammatory and antifibrotic efficacy in the clinical setting. Therefore, while biologically plausible, the clinical utility of HA in this context may be fundamentally constrained by disease chronicity and structural inaccessibility.

Our study also supports prior clinical observations that motor recovery can occur following CTR even in advanced cases with pronounced thenar muscle atrophy. Several authors, including Mondelli et al.,[25] Leite et al.,[26] and Nagaoka et al.,[27] have reported postoperative improvements in thumb opposition and motor conduction despite baseline muscle wasting. Similarly, Park et al.[28] found that even patients lacking preoperative compound motor action potentials could regain motor function after decompression. In our cohort, functional recovery was observed irrespective of the severity of thenar atrophy, with no significant correlation between atrophy grade and clinical improvement. Importantly, the addition of intraoperative perineural HA did not alter this relationship, suggesting that HA does not specifically enhance motor recovery beyond what is achieved through surgical

decompression alone. These findings further imply that thenar atrophy should not be considered a limiting factor in deciding the potential benefit of CTR, with or without adjunctive HA therapy.

Several injectable biologic agents have been explored for the treatment of CTS, each targeting inflammation, fibrosis, or nerve regeneration. PRP, for instance, has shown variable outcomes, with some studies reporting improvements in symptom severity and nerve conduction parameters.[2,5] These effects are attributed to PRP's rich concentration of growth factors, though efficacy depends heavily on preparation protocols and disease severity. Corticosteroid injections remain a mainstay for short-term relief but do not address structural changes and often require repeated administration.[29-31] More recently, 5% dextrose injections have gained popularity as a low-cost, low-risk intervention with anti-inflammatory and neuroregenerative potential. They are primarily used in patients with mild-to-moderate CTS and have demonstrated promising results in early symptom relief and functional improvement. However, their long-term efficacy and comparative benefit over other biologic treatments remain to be clarified through larger, controlled trials.[32-35]

Among these options, HA has attracted attention due to its favorable safety profile and demonstrated anti-inflammatory, antifibrotic, and neuroregenerative effects in preclinical models. Through interaction with the CD44 receptor, HA downregulates pro-inflammatory cytokines promotes M2 macrophage polarization, inhibits fibroblast activation, and helps preserve extracellular matrix integrity.[36-38] Animal studies by Seckel et al.,[16] Wang et al.,[22] and Mekaj et al.[17] have shown that early application of HA in acute nerve injuries can enhance axonal regeneration, reduce scar formation, and improve nerve conduction partly by acting as a viscoelastic spacer that physically prevents perineural adhesions.

However, these promising findings stem largely from acute injury models, which differ substantially from the chronic pathology seen in moderate-to-severe CTS. In CTS, sustained mechanical compression, long-standing ischemia, and extensive subsynovial fibrosis create a hostile microenvironment that may impair HA diffusion, limit receptor interaction, and blunt its therapeutic effects. This fibrotic architecture likely contributed to the lack of clinical benefit observed in our study, where HA was administered intraoperatively in a single dose. Pharmacokinetic limitations also pose a challenge. HA has a short half-life in soft tissue, and without a cross-linked or sustained-release formulation, its therapeutic window may be too brief to elicit lasting anti-fibrotic or neuroregenerative effects.[39] Su et al.[18] suggested that any short-term benefit from HA may be due to its mechanical properties rather than biological modulation a view that aligns with our findings.

Importantly, the limitations encountered with HA are not unique. Other injectables, including corticosteroids, PRP, and dextrose, face similar constraints when used in chronically fibrotic environments. Corticosteroids suppress inflammation transiently but do not affect fibrosis. PRP, while rich in regenerative factors, may be less effective in late-stage disease due to its dependence on the host tissue response. Likewise, although 5% dextrose shows promise for modulating neurogenic inflammation, its role in reversing established structural damage remains uncertain. Despite strong mechanistic rationale, the clinical utility of HA in advanced CTS appears limited by the chronic fibrotic and ischemic tissue environment. Future strategies should focus on optimizing delivery such as using higher-molecular-weight or cross-linked HA, repeat dosing, or combination with other biologics and identifying patient subgroups with less advanced disease who may benefit more from such interventions.

Limitations

There are several limitations to this study that must be acknowledged when interpreting its results. To begin with, its retrospective design inherently limits causal inference and introduces potential risks of selection and information bias. Although demographic and baseline clinical characteristics were well-balanced between the groups, the lack of randomization raises the possibility of residual confounding. Unmeasured variables such as undetected comorbidities, occupation-related repetitive hand use, or inconsistent adherence to postoperative rehabilitation protocols may have influenced clinical outcomes. As these factors were not systematically documented, they could have contributed to variability in symptom resolution or functional recovery that was unrelated to the interventions themselves.

Second, the follow-up period of six months, while sufficient for capturing short- to mid-term recovery, may not adequately reflect the long-term therapeutic effects of HA, particularly in terms of nerve regeneration, reduction of perineural fibrosis, or prevention of symptom recurrence. HA's biological activity may exert delayed effects that extend beyond the timeframe evaluated in this study. Future studies with longer follow-up durations are warranted to determine whether late-phase differences in clinical or electrophysiological outcomes emerge over time.

Third, the intervention involved a single intraoperative administration of HA. In contrast, many preclinical studies demonstrating therapeutic efficacy of HA have utilized repeated applications, higher concentrations, or sustained-release delivery systems to enhance local bioavailability and prolong therapeutic effects. The use of a single-dose protocol in a chronically fibrotic environment may have been insufficient to achieve the intended anti-inflammatory and antifibrotic outcomes. Future investigations should evaluate alternative dosing strategies or delivery mechanisms that better mimic the conditions under which HA has shown benefit in experimental models.

Fourth, this study did not incorporate imaging or biochemical assessments to evaluate perineural fibrosis, nerve edema, or local inflammatory activity. While clinical and electrophysiological parameters provide important outcome data, they may not fully capture the biological mechanisms underlying HA's therapeutic effects—or lack thereof. Incorporating adjunctive tools such as high-resolution

ultrasound, elastography, MRI, or biomarker profiling could offer valuable insights into tissue-level changes and enhance mechanistic interpretation in future studies.

Given these limitations, future research should focus on well-designed, prospective randomized controlled trials with sufficient sample size, extended follow-up periods, and mechanistic outcome measures. These studies should evaluate the clinical potential of various HA formulations as well as alternative delivery strategies, including sustained-release carriers and intra-sheath injection techniques. Additionally, combining HA with other biologic agents, such as corticosteroids, PRP, or antifibrotic compounds, may enhance therapeutic efficacy. Incorporating advanced imaging modalities and biochemical markers of inflammation and fibrosis will further support a mechanistic understanding and enable more precise, personalized treatment strategies. Ultimately, these efforts may help identify optimal applications for HA as an adjunctive therapy in the broader management of CTS, beyond standard surgical decompression alone.

CONCLUSION

This study demonstrated that both standard CTR and CTR combined with intraoperative perineural HA injection led to significant improvements in pain, functional outcomes, and nerve conduction parameters in patients with moderate-to-severe CTS. However, the addition of HA did not result in a statistically or clinically meaningful advantage over CTR alone.

Although HA possesses a favorable biological profile and has shown promise in preclinical models of acute nerve injury, its therapeutic impact in chronic compressive neuropathies may be limited. The fibrotic and ischemic microenvironment characteristic of advanced CTS likely impairs HA diffusion, retention, and its ability to modulate inflammation and tissue remodeling.

Nonetheless, further prospective studies are warranted to investigate whether alternative delivery strategies, repeated applications, or use in earlier disease stages could enhance its clinical efficacy. Identifying patient subgroups with less fibrotic disease or different pathophysiological profiles may also help clarify HA's role within the broader framework of biologic adjuncts in peripheral nerve decompression.

Until such evidence becomes available, the intraoperative use of HA during CTR should be regarded as investigational rather than standard practice.

ETHICAL DECLARATIONS

Ethics Committee Approval

Approved by the Bursa City Hospital Scientific Researches Ethics Committee (Date: 05.03.2025, Decision No: 2025-5/2).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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